REMARKS

These remarks are in Response to the Office Action mailed April 24, 2006. Claims 10, 12, 14, 19, 20, 25, 31, 34 to 39, 41 and 42 have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. Accordingly, upon entry of the Response, claims 1 to 4, 6 to 8, 13, 15, 16 to 18, 21, 23, 24, 28, 29 32 and 40 are under consideration.

Regarding the Amendments to the Claims

The amendments to the claims are supported throughout the specification or were made to address an informality. In particular, the amendment to claim 1 to recite administering "intravenously or intraperitoneally" is supported, for example, at page 10, lines 11-12. The amende to recite "from" was made in order to comply, with the Examiner's request. Thus, as the amendments are supported by the specification or was made to address an informality, no new matter has been added and entry thereof is respectfully requested.

I. CLAIM OBJECTIONS

Claims 8 and 17 stand objected to due to the numbering of the claims from which they depend. Claims 1 to 4, 6 to 8, 10, 12, 13, 15 to 21, 23 to 25, 28, 29, 40 and 41 stand objected to due to grammar of a particular phrase.

Claim 8 depends from claim 3. Accordingly, Applicants believe that the ground for rejection does not apply to claim 8. Claim 17 depends from claim 40. Claim 17 will be renumbered upon notification of allowable subject matter. The remaining claims have been amended as suggested by the Examiner. Accordingly, the grounds for objection are moot and Applicants respectfully request that the objection be withdrawn.

II. REJECTION UNDER 35 U.S.C. §102(e)

The rejection of claims 12 to 18, 21, 23, 25, 29, 31 to 36, 39 and 40 under 35 U.S.C. §102(e) as allegedly anticipated by Conti-Fine (U.S. Patent No. 6,929,796) is respectfully

traversed. Allegedly, Conti-Fine teaches each and every element of the rejected claims. [see Office Action, page 3]

Claims 12 to 18, 21, 23, 25, 29, 31 to 36, 39 and 40 are not anticipated by Conti-Fine (U.S. Patent No. 6,929,796). Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claims 10, 12, 14, 19, 20, 25, 31, 34 to 39, 41 and 42 have been cancelled herein without prejudice and the claims have been amended as set forth above. The rejection will therefore be addressed as it may relate to claims 13, 15 to 18, 21, 23, 29, 32 and 40 upon entry of the Response.

The amended claims are directed to, *inter alia*, methods of reducing or preventing formation of inhibitory antibodies to a blood coagulation protein delivered to a mammal by way of gene therapy, wherein said mammal has a genetic defect which can result in generation of inhibitory antibodies to the protein or blood coagulation protein, said method comprising administering to said mammal cyclophosphamide prior to or simultaneously with said gene therapy before formation of said inhibitory antibodies. Conti-Fine fail to teach or suggest such a method. In particular, for example, among other things Conti-Fine fail to mention cyclophosphamide, let alone teach or suggest the claimed methods. Accordingly, as Conti-Fine (U.S. Patent No. 6,929,796) fail to teach each and every element of claims 13, 15 to 18, 21, 23, 29, 32 and 40, the claims are not anticipated under 35 U.S.C. §102(e), and Applicants respectfully request that the rejection be withdrawn.

III. REJECTION UNDER 35 U.S.C. §103(a)

The rejection of claims 1 to 4, 6 to 8, 10, 12 to 21, 23 to 25, 28, 29 and 31 to 41 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) taken with Conti-Fine (U.S. Patent No. 6,929,796) is respectfully traversed. The grounds for rejection are set forth in the Office Action mailed April 24, 2006, pages 4-7.

Claims 10, 12, 14, 19, 20, 25, 31, 34 to 39, 41 and 42 have been cancelled without prejudice and the claims have been amended as set forth above. The rejection will therefore be addressed as it may relate to claims 1 to 4, 6 to 8, 13, 15, 16 to 18, 21, 23, 24, 28, 29 32 and 40 upon entry of the Response.

In order for a rejection to be proper under 35 U.S.C. §103, *inter alia*, there must have been at the time of the invention 1) a suggestion or motivation to modify or combine the references at the time of the invention; 2) a reasonable expectation of success of producing the claimed invention; and 3) the combined references must teach or suggest each and every claim limitation. Both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988).

Furthermore, the prior art must be considered in its entirety....including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). In addition, objective evidence of non-obviousness must be considered. *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983); *see also*, *In re Corkill*, 711 F.2d 1496 (Fed. Cir. 1985).

Here, *inter alia*, 1) the skilled artisan would not have had a reasonable expectation of success at the time of the invention in view of the art; and 2) the prior art teach away from the claimed invention. Furthermore, objective evidence of non-obviousness of claims 1 to 4, 6 to 8, 13, 15, 16 to 18, 21, 23, 24, 28, 29 32 and 40, in the form of unexpected results, is submitted herewith.

In terms of a reasonable expectation of success at the time of the invention, the scientific literature is replete with studies in which immune-suppressive agents either failed completely, caused unacceptable adverse side effects, or was limited in duration and effectiveness. As an example, the cited Wilson *et al.* patent reports studies using CD4 antibodies and CD40L antibodies for immunosuppression. In both studies, neutralizing antibodies formed anyway (column 18, lines 52-56; column 22, Table III; and column 23, lines 22-28). In the previously cited Warrier *et al.* reference (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)), the authors state that "Eradication of the inhibitor by immune tolerance induction (ITI) has only been minimally effective" (page S125, abstract). In the previously cited Nilsson *et al.* reference (Proc. Natl. Acad. Sci. USA 83:9169 (1986)), the authors state that "treatment with factor IX and cyclophosphamide was ineffective, resulting in high and persistent anamnestic response." (see page 9173, first sentence under "*Discussion*"). In the previously cited Tengborn reference

(Haemophilia 4:56 (1998)), in 2 patients treated with FIX, cyclophosphamide and gammaglobulin (IV), inhibitory antibodies continued to form and the authors concluded that the treatment had failed (abstract). In the previously cited Fang *et al.* reference (Human Gene Therapy 6:1039 (1995)), dogs administered FIX and cyclosporin A continued to form anti-adenovirus antibodies (page 1043, Fig. 3). In the previously cited Trapnell *et al.* publication (WO 97/39776), mice were administered lacZ vector with various immunosuppressive agents, but neutralizing antibodies formed in several animals administered cyclophosphamide and dexamethasone, but not in deoxyspergualin (DSG) treated animals (Table 1, pages 36 and 37). Thus, in view of the foregoing, it is clear that the art is replete with studies of immunosuppressive agents failing to reduce or prevent formation of inhibitory antibodies in a wide variety of contexts. Consequently, in view of the art, the skilled artisan would not have had a reasonable expectation of success at the time of the invention.

Moreover, Applicants again respectfully remind the Patent Office that the prior art must be considered in its entirety, including portions that teach away. As set forth in the record, at least Tripathy *et al.* (Nat. Med. 2:545 (1996)), and Herzog *et al.* (Blood 90, part 1, Supp. 1, abstract 1057 (1997)) teach away from producing the claimed methods.

Tripathy *et al.* report that mice injected with adenovirus harboring human EPO developed anti-EPO antibodies whereas mice injected with adenovirus harboring murine EPO did not develop anti-EPO antibodies. The fact that Tripathy *et al.* teach that an immune response was not produced against a protein delivered by way of gene therapy that is the same species as the mammal to which it is delivered means that the skilled artisan would be taught away from administering cyclophosphamide prior to or simultaneously with gene therapy to deliver a blood coagulation protein that is the same species as the mammal.

Herzog (Blood) reports that antibodies against Factor IX following injection with an AAV vector with canine Factor IX into a hemophiliac dog (hemophilia B) were not detected. Consequently, Herzog (Blood) teaches the skilled artisan away from administering cyclophosphamide prior to or simultaneously with gene therapy to deliver a blood coagulation protein that is the same species as the mammal.

Exhibits A to D were previously submitted as corroborating evidence that human or canine subjects with hemophilia A or hemophilia B, including subjects incapable of producing

endogenous Factor IX or Factor VIII, did not produce detectable inhibitors against Factor IX (Exhibits A and B, Manno et al., Blood 101:2963 (2003), and Mount et al. Blood 99:2670 (2002), respectively) or Factor VIII (Exhibits C and D, Roth et al., N. Engl. J. Med. 344:1735 (2001), and Powell et al., Blood 102:2038 (2003), respectively). Exhibits A to D therefore corroborate that the skilled artisan would not have administered cyclophosphamide prior to or simultaneously with gene therapy to deliver a blood coagulation protein that is the same species as the mammal.

In contrast to the art being replete with reports of immunosuppressive agents failing to reduce or prevent formation of inhibitory antibodies, the claimed methods result in reducing or preventing formation of inhibitory antibodies to a blood coagulation protein long-term and without significant adverse side effects. In support of Applicants' position, submitted herewith is a data summary of 10 dogs treated in accordance with the claimed methods which were followed up to 3.5 years (Exhibit A). Dog D99 was followed for 39 months since receiving cyclophosphamide with Factor IX gene therapy. Dog F57 was followed for 27 months since receiving cyclophosphamide with Factor IX gene therapy. Dog F57 was followed for 8 months since receiving cyclophosphamide with Factor IX gene therapy. Two dogs, H34 and H48, have been followed for 723 days since receiving cyclophosphamide with Factor IX gene therapy. Dogs I04 and I05 have been followed for about 1.5 years since receiving cyclophosphamide with Factor IX gene therapy. Dogs I07 and J04 have been followed for over one year since receiving cyclophosphamide with Factor IX gene therapy. Dog E59 was initially used as a control but then received cyclophosphamide with Factor IX gene therapy and subsequently followed for 281 days.

In all 10 of the dogs that received cyclophosphamide with Factor IX gene therapy, no inhibitory antibodies against FIX have been detected, based on activated partial thromboplastin time (aPTT) readout or ELISA, and levels of FIX expression have been maintained throughout the time period in question (Exhibit A, Duration). Furthermore, none of the dogs exhibited significant adverse side effects. In contrast, two of three dogs, J62 and E60, that did not receive cyclophosphamide with Factor IX gene therapy produced inhibitory antibodies against FIX (Exhibit A). Accordingly, the claimed methods, which can achieve a long-term reduction or prevention of inhibitory antibodies are in stark contrast to the art of record discussed above.

Consequently, the claimed methods achieve unexpected results in view of the art of record. Applicants submit that these unexpected results constitute objective evidence of non-obviousness of claims 1 to 4, 6 to 8, 13, 15, 16 to 18, 21, 23, 24, 28, 29 32 and 40, which must be considered under 35 U.S.C. §103(a).

In sum, in the view of the absence of a reasonable expectation of success at the time of the invention, that the scientific literature includes a number of references that teach away from the claimed invention, and the unexpected results compared to the art of record, claims 1 to 4, 6 to 8, 13, 15, 16 to 18, 21, 23, 24, 28, 29 32 and 40 would not have been obvious over Wilson *et al.* (U.S. Patent No. 6,251,957) or Conti-Fine (U.S. Patent No. 6,929,796) alone, or in combination, at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 4, 6 to 8, 13, 15, 16 to 18, 21, 23, 24, 28, 29 32 and 40 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

Date: 10-23-06

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CERTIFICATION UNDER 37 C.F.R. §§ 1.8 and/or 1.10*

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I hereby certify that, on the date shown below, this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Signature

Date: October 23, 2006

PATRICIA MUNOZ
(type or print name of person certifying)

** Only the date of filing (§ 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under § 1.8 continues to be taken into account in determining timeliness. See § 1.703(f). Consider "Express Mail Post Office to Addressee" (§ 1.10) or facsimile transmission (§ 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.*

EXHIBIT A

Summary of FIX Expression and Inhibitor Formation Data in Dogs

	Cyclophosphamide Treatment	# times aPTT tested	Duration (days or months)	Inhibitor formation based on aPTT readout	Inhibitor formation based on ELISA readout
H34	Yes	34	723 days	No	No (19 tests over 253 days)
H48	Yes	33	723 days	No	No (18 tests over 254 days)
I04	Yes	28	527 days	No	No (17 tests over 197 days)
I07	Yes	30	366 days	No	No (8 tests over 133 days)
I05	Yes	32	562 days	No	No (8 tests over 133 days)
J04	Yes	24	378 days	No	N/A
E59[@]	Yes	22	281 days	No	
D99	Yes		39 months	No	
F57*	Yes		27 months	No	
H08*	Yes		8 months	No	
J03	No	15	114	No	
J62	No	16	85	yes	
E60*	No			yes	

*Results published in Arruda et al., Blood 105:3458 (2005).
@ E 59 was also used as a control in Arruda et al., Blood 105:3458 (2005), but subsequently received cyclophosphamide with a re-injection of Factor IX gene.